

The use of hormonal contraceptives in fertility treatments: a committee opinion

Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Washington, D.C

The use of hormonal contraception can be considered to aid in the timing of assisted reproductive technology cycles, reduce the risk of ovarian cysts at in vitro fertilization cycle initiation, and optimize visualization before hysteroscopy. (Fertil Steril® 2024;■:■-■. ©2024 by American Society for Reproductive Medicine.)

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Hormonal contraception has several indications in gynecology beyond the prevention of pregnancy. Hormonal contraception is frequently used in reproductive medicine for indications, such as ovarian cyst prevention, preoperative management, and hormone replacement. It is used in the treatment of reproductive disorders such as endometriosis, polycystic ovary syndrome (PCOS), and hirsutism. Noncontraceptive benefits also include menstrual management, such as the treatment of dysmenorrhea, menorrhagia, and menstrual irregularity (1). Many of these topics are covered more extensively in other American Society for Reproductive Medicine Practice Committee publications (2), and only indications related to fertility treatments will be covered here.

Although hormonal contraception is frequently used in the management of reproductive issues for women, it is also heavily relied on in the context of fertility treatments. A unique use of hormonal contraception within infertility treatment is hormonal

pretreatment for in vitro fertilization (IVF). Hormonal contraceptive pretreatment includes menstrual cycle control, synchronization of the oocyte cohort, modification of the hormonal milieu before controlled ovarian stimulation (COS) for IVF, and suppression of ovarian cyst formation. Hormonal contraception can also be used as a pretreatment tool before hysteroscopy for fertility-related surgeries.

The impact of hormonal contraception on ovarian stimulation has been extensively studied, with investigation focusing on the type of hormonal contraception used, effect of the duration of hormonal contraception pretreatment, and concomitant use with different reproductive disorders. Studies have focused on outcomes, including oocyte yield, pregnancy, and live birth (LB) rates. Hormonal contraception may impact the markers of ovarian reserve. Therefore, these tests should be interpreted with caution while a woman is on hormonal contraception and counseling modified. Several factors should be

considered before placing patients on hormonal contraception in the setting of fertility treatments and, in some cases, alternatives used.

HOW DOES HORMONAL CONTRACEPTION AFFECT TIMING OF ASSISTED REPRODUCTIVE TECHNOLOGY CYCLES?

Although COS for IVF classically begins with menses, hormonal contraception allows for the scheduling of an IVF cycle. This can be beneficial for both the patient and clinic. Some IVF clinics will use hormonal contraception to “batch” IVF cycles or have several patients complete their IVF cycles at the same time. Additionally, hormonal contraception can be used in third-party reproductive cycles to coordinate the oocyte donor with the oocyte recipient. Hormonal contraception also plays a pivotal role in reducing the risk of cancellation of cycles from unintended pregnancy in the donor (3).

The European Society of Human Reproduction guidelines on ovarian stimulation for IVF/intracytoplasmic sperm injection reinforce that the use of estrogen and progesterone for scheduling is probably acceptable on the basis of safety and efficacy data,

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although evidence surrounding the use of pretreatment hormonal contraception has been inconsistent (4).

DOES HORMONAL CONTRACEPTION IMPACT THE STIMULATION YIELD OF AN IVF CYCLE?

The suppressive nature of hormonal contraception on circulating follicle-stimulating hormone (FSH) and luteinizing hormone may be beneficial for synchronization of the oocyte cohort during COS; however, the suppression may also attenuate the ovarian response to gonadotropins (5). In young patients, high androgenic hormonal contraception exposure may suppress ovarian responsiveness and oocyte yield (6). In a prospective randomized study of hormonal treatment before IVF, women using hormonal contraception required more gonadotropins than women without hormonal pretreatment; however, there was no adverse effect on oocyte yield or pregnancy outcomes (5). Subsequently, a meta-analysis of 4 randomized controlled trials (RCTs) demonstrated that the ongoing pregnancy rate (odds ratio, 0.74) and oocyte yield were similar for women with pretreatment hormonal contraception vs. no pretreatment hormonal contraception in gonadotropin-releasing hormone (GnRH) antagonist cycles. The duration of treatment (weighted mean difference, +1.41 days; 95% confidence interval, +1.13 to +1.68) and total gonadotropin dose (weighted mean difference, +542 IU; 95% confidence interval, +127 to +956) were significantly higher in the hormonal contraception pretreatment group (7).

Overall, there is no overwhelming evidence to suggest that hormonal contraception significantly decreases ovarian stimulation response. When determining whether to pursue hormonal contraception pretreatment, the important factors to consider include patient age, ovarian reserve, and IVF protocol type. In addition, the duration of hormonal contraception may be considered; however, there is no evidence to suggest the timing and length of pretreatment with hormonal contraception influence assisted reproductive technology (ART) outcomes.

DOES THE TYPE OF HORMONAL CONTRACEPTION USED DIFFERENTIALLY AFFECT OVARIAN STIMULATION?

Some studies have suggested that any potential detrimental effect of hormonal contraception on oocyte yield is related to the progestin component (6). Specifically, progestins with greater androgenic properties, such as estrane- and gonane-derived progestins, may be associated with decreased oocyte yield and lower antimüllerian hormone (AMH) levels than those constituting antiandrogenic hormonal contraception, such as drospirenone, dienogest, and trimegestone (6). This may be because of androgens working synergistically with FSH in early follicular development and then inhibiting gonadotropin support of the growing follicles, followed by atresia of the growing follicles because of a lack of FSH (6). A small study has compared egg donors on “androgenic” hormonal contraception pretreatment before stimulation (containing norethindrone, norgestimate, and norgestrel) with those without hormonal contraception pretreatment. Donors

on androgenic hormonal contraception demonstrated a significantly lower egg yield than those without hormonal contraception (hormonal contraception, 11.3 oocytes; no hormonal contraception, 16.6 oocytes; $P < .05$) (8). Nonetheless, a recently published retrospective analysis by Montoya-Botero et al. (9) found no significant difference in the clinical pregnancy or LB rate between women taking hormonal contraception containing the third-generation progestin desogestrel and those taking fourth-generation progestin drospirenone before COS for IVF.

There is a lack of consistent evidence to make a recommendation for a formulation of hormonal contraception being less suppressive for patients planning to undergo COS for ART.

DOES PRETREATMENT WITH HORMONAL CONTRACEPTION IMPACT THE LB RATE OF IVF CYCLES?

Pretreatment with hormonal contraception in antagonist and agonist cycles has been associated with a reduction in the LB rate in some studies. In a retrospective cohort study, pretreatment with hormonal contraception was associated with a reduction in the LB rate after fresh transfer (42.6% vs. 52.8%, $P < .001$), as well as the cumulative LB rate (62.8% vs. 67.6%, $P = .01$) (10). However, it has also been demonstrated that hormonal contraception administration for an interval of 12–30 days with a 5-day washout period does not affect clinical pregnancy, LB, or cumulative LB in patients undergoing COS for an IVF cycle (9). Additionally, a 2017 Cochrane Review of 29 RCTs in GnRH agonist and antagonist cycles found no clear evidence of a difference in the pregnancy or LB rates. In antagonist cycles, hormonal contraception was associated with a decreased risk of pregnancy loss (3).

WHAT ABOUT THE IMPACT OF OTHER TYPES OF HORMONAL CONTRACEPTION ON IVF SUCCESS?

A related issue is the impact of a levonorgestrel-releasing (LNG) intrauterine device (IUD) on ovarian stimulation. A patient may have an LNG-IUD for contraception and management of endometriosis or abnormal bleeding and be pursuing elective egg or embryo freezing. Providers also often face this question in the egg donor population. Thus, providers need to recognize the potential impact of the LNG-IUD on ovarian stimulation. Adeleye et al. (11) performed a retrospective cohort evaluating oocyte yield in women with a 52-mg LNG-IUD compared with that in subjects without an IUD. Subjects with an LNG-IUD had a lower peak estradiol level and required a higher FSH dose per cycle. No differences in the total or mature oocyte yield were noted in subjects with or without LNG-IUD. Furthermore, no differences in blastocyst progression or the fertilization, clinical pregnancy, or LB rates were observed in recipients of donor oocytes who had a LNG-IUD in place during COS. Thus, egg donors or patients considering fertility preservation can retain their LNG-IUD before and during ovarian stimulation. However,

providers should note a potential higher dose of FSH and, thus, cost. The impact of an etonogestrel implant during ovarian stimulation was similarly described in a case report. However, given the limited data and higher systemic progesterone dosing with an implant, a definitive recommendation cannot be made (12).

DOES PRETREATMENT HORMONAL CONTRACEPTION IMPACT THE LB RATE AMONG WOMEN IN SPECIAL POPULATIONS?

Diminished ovarian reserve

Data are limited regarding the potential impact of hormonal contraception pretreatment on IVF outcomes in women with diminished ovarian reserve (13). A retrospective analysis compared poor responder patients pretreated with hormonal contraception vs. natural cycle start in agonist-flare cycles and found no difference in the implantation or pregnancy rates. Randomized trials in this population are not available.

Polycystic ovary syndrome

Pretreatment hormonal contraception in women with PCOS may significantly aid in regulating menses and synchronizing follicular development; however, clinical trials have demonstrated mixed results surrounding ART outcomes (14, 15). This may be because of differing lengths of pretreatment hormonal contraception exposure. Pan et al. (14) studied the impact of 3 consecutive months of hormonal contraception before IVF in subjects with PCOS. They found improved implantation and clinical pregnancy rates in subjects using at least 3 months of hormonal contraception compared with those in non-oral contraceptive pill (OCP) users and those using <2 months of hormonal contraception. These subjects were also found to have a lower antral follicle count (AFC) and reduced symptoms of hyperandrogenism while on hormonal contraception. The benefit of a 3-month course of hormonal contraception may be, in part, related to the 70–90-day development of the ovarian secondary follicles to periovulation (16).

Conversely, other studies have demonstrated adverse effects of hormonal contraception pretreatment on the LB rate after fresh embryo transfer in women with PCOS. In a nested cohort study and secondary analysis of a multicenter randomized trial, Wei et al. (15) found that subjects with PCOS exposed to hormonal contraception for 21–25 days before GnRH antagonist protocol IVF had lower rates of clinical pregnancy (48.8% vs. 63.6%; relative risk [RR], 2.13) and LB (36.1% vs. 48.1%; RR, 0.75) after a fresh embryo transfer than those with spontaneous menses. Interestingly, they also found that women with hormonal contraception-induced menses in frozen embryo transfer cycles within this patient population had a similar pregnancy rate but a higher pregnancy loss rate (27.7% vs. 13%; RR, 2.13) than those with spontaneous menses.

It is important to consider the potential role for mitigating the risk of ovarian hyperstimulation syndrome in patients with PCOS because hormonal contraception pretreatment

has been shown to moderately reduce ovarian high response without influencing the quality of oocytes (17).

Endometriosis

There is existing evidence that women with endometriosis may benefit from pretreatment hormonal contraception, specifically pertaining to improved pregnancy rates per retrieval (18, 19). This may be because of ovarian suppression inhibiting the production of inflammation-mediated aromatase expression and estradiol production, which may also have downstream effects on morphological and functional changes in the endometrium (20, 21).

One study by de Ziegler et al. (22) demonstrated that a 6–8-week course of hormonal contraception pretreatment in women with endometriosis resulted in higher pregnancy rates per retrieval and fresh embryo transfer than controls (35% vs. 12.9%) and that the effect was even more robust when endometriomas were present. More research is required to determine whether this effect is a result of endometrial receptivity, oocyte quality, or other effects and whether these results are consistent in multiple studies.

CAN HORMONAL CONTRACEPTION BE USED IN OVARIAN CYST MANAGEMENT BEFORE FERTILITY TREATMENTS?

Ovarian cyst formation is a common problem in reproductive-aged women. In a large cross-sectional study, ovarian cysts with a diameter of >30 mm were noted in 4%–7% of women during ultrasound evaluation before initiating an oral contraceptive (23). Functional ovarian cysts may be follicular or corpus luteum cysts and secrete estradiol or progesterone. These cysts may cause irregular menstrual bleeding, pain, inhibition of response to ovarian stimulation, and an increased risk of ovarian torsion. Nonfunctional ovarian cysts do not secrete hormones.

The impact of an ovarian cyst at the start of IVF stimulation is controversial. An early study suggested a negative impact of ovarian cyst formation on IVF outcomes (24). The investigators noted an increase in cycle cancellation likely because of premature luteinizing hormone surge with cysts 16–29 mm and poor response to stimulation with cysts 30–60 mm (24–26). Subsequent studies have suggested no impact of baseline ovarian cysts on the number of follicles aspirated or oocytes retrieved with IVF. Notably, patients were excluded if the cystic structure was >50 mm and/or if the cycle day 3 estradiol level was >50 pg/mL. Despite a lack of impact on mature oocytes retrieved, patients with nonfunctional ovarian cysts required increased gonadotropin dosing and had lower peak estradiol levels. Additionally, patients with unilateral cystic structures had significantly fewer follicles from the cystic ovary than from the contralateral ovary. These findings led the investigators to suggest that a nonfunctional ovarian cyst induces changes in the intraovarian endocrine environment to interfere with follicular development and function. Additional studies have had inconsistent findings. Despite these conflicting findings, most providers will avoid or

postpone a fertility treatment cycle if a large or functional ovarian cyst is present at baseline evaluation (27–31).

Christensen et al. (32) noted a lower prevalence of ovarian cysts in women using hormonal contraception than in those not using contraception or using a non-hormone-releasing IUD (RR, 0.22; 95% CI, 0.13–0.39). The incidence of ovarian cysts in women not on contraception was 9.5% (14/147) vs. 2.4% (5/211) in women who were on hormonal contraception for at least 3 months.

Because of the known decreased risk of ovarian cysts in women on hormonal contraception, they are often initiated to hasten the resolution of functional cysts to allow resumption of fertility treatment. However, a Cochrane Review (33) published in 2014 refuted this recommendation after evaluating 8 RCTs comparing hormonal contraception with expectant management for cyst treatment. To our knowledge, no study demonstrated a benefit of hormonal contraception over expectant management. Resolution occurred spontaneously within 4–6 weeks in the large majority of patients, whether treated with hormonal contraception or expectantly managed. Those that persisted were often pathologic (endometrioma, hydrosalpinx, dermoid cyst, and paraovarian cyst) and less likely a functional ovarian cyst.

On the basis of this available information, hormonal contraception should not be started to hasten the resolution of ovarian cysts but can be protective against the development of new ovarian cysts.

CAN HORMONAL CONTRACEPTION BE USED TO AID IN THE EVALUATION OF THE UTERINE CAVITY BEFORE FERTILITY TREATMENTS?

Hysteroscopy is frequently used in reproductive medicine to evaluate and treat uterine pathology for optimization before fertility treatments. Hysteroscopy is ideally performed when the endometrial lining is relatively thin, such as in the early follicular phase, just after the cessation of menses. A thickened endometrium can impair visualization of smaller lesions and easily breaks off or bleeds further diminishing visualization.

Scheduling of hysteroscopic procedures in the appropriate time frame can be difficult, particularly for patients with irregular menses or prolonged menstrual bleeding. Additional benefits of hormonal contraception use in this population include the prevention of pregnancy and ease of scheduling for surgery.

It is important to note that hormonal contraception most reliably prevents ovulation and, therefore, will more likely result in a thin endometrium when started early in the menstrual cycle. One study noted no ovulation when hormonal contraception was started when the maximum follicle diameter was 10 mm (mean cycle day 7.6) or lower or when the vaginal ring was started at a follicle diameter of 13 mm (median cycle day 11) or lower. Additionally, starting the menstrual cycle on day 1 vs. 5 led to fewer dominant follicles (34). In 2006, Grow and Iromloo (35) demonstrated that initiation of combination OCPs on menstrual cycle days 1–3 consistently maintained a thinner endometrium (4.1 mm)

than starting in the late follicular phase (11 mm) or late luteal phase (12 mm).

Multiple other hormonal preparations, including norgestrel acetate (36), oral desogestrel plus vaginal raloxifene (37), estradiol plus dienogest (38), gestrinone (39), and desogestrel alone (40), appear to demonstrate benefit for rapid endometrial preparation before operative hysteroscopy.

HOW DOES HORMONAL CONTRACEPTION AFFECT OVARIAN RESERVE MARKERS BEFORE INITIATING AN IVF CYCLE?

Ovarian reserve markers, such as AMH and the AFC, have been shown to be suppressed in response to prolonged hormonal contraception (41). One study has suggested a decrease of 30% in both the AMH level and AFC with long-term hormonal contraception (>6 months) (42). In a longitudinal study of >700 women, the AFC after cessation of hormonal contraception started to increase at 1 month and plateaued at 6 months, suggesting nearly 6 months for recovery of the AFC to pre-hormonal exposure (43). Eighty percent of women in this study had an increase in the AFC after stopping hormonal contraception, with 60% of women achieving normalization of the AFC. Subgroup analyses suggested that this was only observed in women with a low AFC on hormonal contraception. Women with a normal AFC on hormonal contraception were unlikely to observe an increase in the AFC when stopping hormonal contraception (43).

Cessation of hormonal contraception for 2–3 months may allow for a more accurate assessment of a patient's ovarian reserve, as exhibited by either the AMH level or AFC.

WHAT SHOULD PROVIDERS BE AWARE OF BEFORE USING HORMONAL CONTRACEPTION IN FERTILITY PATIENTS?

It is imperative that providers are aware of the eligibility criteria for combined hormonal contraceptive use outlined in the US Medical Eligibility Criteria, as well as the RRs of therapy in certain populations (44). Although most patients undergoing fertility treatment are at low risk of complications, certain medical comorbidities should be considered, including advanced age, smoking status, a history of migraine with aura, increased risks of venous thromboembolic events, and cardiovascular disease.

Migraines with aura are common in reproductive-aged women. Such a history, when present, needs to be elicited before initiating combination hormonal contraception (those containing both estrogen and progesterone). The World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception from 1999 (45) demonstrated that women with a history of migraine on combination hormonal contraception had 3 times higher odds of ischemic stroke than those with a history of migraine not on combined hormonal contraceptive. They noted a higher OR of 3.81 for migraine with aura and an OR of 2.97 for migraine without aura. The coexistent use of combined hormonal contraception or history of hypertension or smoking had

greater than multiplicative effects on the OR for ischemic stroke associated with migraine alone.

There is some thought that the short-term use of combined hormonal contraception (3–6 weeks) immediately before ovarian stimulation confers a decreased risk of complications (e.g., venous thromboembolism [VTE]) compared with the more long-term use for contraception. Although data for such short-term use are limited, there is evidence to support that the longer duration of use actually decreases some risks, such as VTE (46). This case-control study reported that the risk of VTE among current OCP users significantly decreased over time from an OR of 5.1 at <1 year to 2.1 after >5 years. There are data to support a significant impact of hormonal contraception on the coagulation system as early as 6 weeks of use. Low-dose hormonal contraception caused an increase in the levels of factors VII and X, plasminogen, fibrinogen, and D-dimer. Antithrombin II and protein C activities did not change over the study period. These investigators reported a reduced effect with a 20- μ g pill compared with that with a 30- μ g pill (47). Therefore, the short-term use does not appear to minimize the risks of hormonal contraception, although the periods of 1–2 weeks as often used in pretreatment for fertility treatments have not been specifically studied. However, it should be acknowledged that pregnancy itself is a significant risk factor for VTE and that the short-term use of OCPs before IVF stimulation would be expected to confer a lower risk than pregnancy itself.

Some patients may be concerned about adverse side effects noted with hormonal contraceptive use. These concerns have led to substantial changes in the makeup of hormonal contraception over time, such as a decrease in the estrogen dosage, new progestin components, and new sequences of administration (48). In a study from 2007, the most common symptoms in a population of French women using hormonal contraception were weight gain (25.2%), painful menses (20.7%), swollen legs (20.9%), and heavy menstrual bleeding (15.6%). Women using progestin-only pills and second-generation progestins were more likely to report irregular or breakthrough bleeding. The investigators found no evidence to support that decreasing the estrogen dosage decreases any symptom associated with the hormonal contraception. Although patients may have concerns about these side effects, it is worth noting that short-term use with fertility treatments will likely minimize potential side effects (48).

ARE THERE ALTERNATIVES TO HORMONAL CONTRACEPTION THAT CAN BE USED WITH FERTILITY TREATMENTS?

One alternative to combination hormonal contraception in those patients with risk factors for use is the progesterone-only pill (POP). Available evidence demonstrates that POP use does not increase the risk of ischemic stroke in patients with menstrual migraines (49) and, therefore, may be an acceptable alternative. However, data on the potential adverse outcomes with the POP are limited (Centers for Disease Control and Prevention). There are certain circumstances where POP use should also be approached cautiously. Women with hypertension using a POP have a slightly increased risk

of cardiovascular events compared with those not using this method. It is also contraindicated in patients with active or recent (<5 years) breast cancer.

The disadvantages of the POP in reproductive medicine include a higher risk of irregular vaginal bleeding and functional ovarian cysts. Approximately 20%–30% of users experience intermenstrual bleeding or spotting, which is a common reason for discontinuation (50). This abnormal bleeding is most frequent on initiation and is likely because of incomplete ovarian suppression. In a study of 21 women who had been using a POP for at least 6 months, functional cysts were noted in 8 on initial examination. Four of the 13 women without cysts on baseline examination subsequently went on to develop new functional cysts associated with symptoms in 2 of these women (51). The use of POP before IVF is less likely to suppress cyst formation or premature follicular development.

SUMMARY

- Hormonal contraception pretreatment can be used for scheduling IVF treatments.
- There are inconsistent data that pretreatment with hormonal contraception impacts ovarian stimulation, although it may increase the amount of gonadotropins required.
- There is inconsistent evidence that the formulation of hormonal contraception impacts IVF outcomes.
- The use of hormonal contraception in the setting of PCOS or endometriosis is conflicting, and thus, definitive conclusions cannot be drawn.
- The use of hormonal contraception for the suppression of ovarian cyst has not been substantiated.
- Treatment with hormonal contraception can be used before hysteroscopy in the workup of infertility.
- The use of hormonal contraception may decrease markers of ovarian reserve, and those markers may improve after cessation of hormonal contraception for some patients, especially for those women with low AFCs.

When the use of hormonal contraception is contraindicated, POP may be used as an alternative.

CONCLUSIONS

- The use of hormonal contraception can be considered to aid in the timing of ART cycles, reduce the risk of ovarian cysts at IVF cycle initiation, and optimize visualization before hysteroscopy.
- Long-term hormonal contraception can falsely lower markers of ovarian reserve, and consideration should be given to stopping therapy to re-evaluate the baseline levels.

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This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine (ASRM) as a service to its members and other practicing clinicians. Although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved

standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations. The Practice Committee and Board of Directors of the ASRM have approved this report.

Declaration of Interests

This document was reviewed by the ASRM members, and their input was considered in the preparation of the final document. The following members of the ASRM Practice Committee participated in the development of this document: Clarisa Gracia, M.D., M.S.C.E.; Alan Penzias, M.D.; Paula Amato, M.D.; Jacob Anderson, M.B.A.; Kristin Bendikson, M.D.; Tommaso Falcone, M.D.; Rebeca Flyckt, M.D.; Jessica Goldstein, R.N.; Karl Hansen, M.D., Ph.D.; Micah Hill, D.O.; Sangita Jindal, Ph.D.; Suleena Kalra, M.D., M.S.C.E.; Tarun Jain, M.D.; Bruce Pier, M.D.; Michael Thomas, M.D.; Richard Reindollar, M.D.; Jared Robins, M.D.; Chevis N. Shannon, Dr.Ph., M.B.A., M.P.H.; Anne Steiner, M.D., M.P.H.; Cigdem Tanrikut, M.D.; and Belinda Yaeger, M.D. The Practice Committee acknowledges the special contribution of Kristin Bendikson, M.D.; Belinda Yaeger, M.D.; Megan Sax, M.D.; and Brooke Rossi, M.D., in the preparation of this document. All Committee members disclosed commercial and financial relationships with manufacturers or distributors of goods or services used to treat patients. The members of the Committee who were found to have conflicts of interest based on the relationships disclosed did not participate in the discussion or development of this document.

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